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WITNESS my hand this Fourth day of June 1999

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AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: **TASTE-MASKED PHARMACEUTICAL COMPOSITIONS**

Applicant: F. H. FAULDING & CO. LIMITED

The invention is described in the following statement:

Taste Masked Pharmaceutical Compositions

The present invention relates to a pharmaceutical composition, in particular to a taste masked pharmaceutical composition capable of sustained release having improved release characteristics and coating characteristics. The present invention also includes a method of preparing such a composition preferably incorporating a spray drying technique.

Many pharmaceutical drugs have unpleasant tastes and therefore the oral administration of the pharmaceutical drug is often an unpleasant experience, particularly for those who find it difficult to swallow whole dosage forms. The pharmaceutical drug remains in the mouth for a time sufficient to impart its unpleasant taste sometimes resulting in the patient expelling the dosage form.

Artificial flavourings and sweeteners have often been used to mask the taste by generally overwhelming the taste of the pharmaceutical. However, these are often unsuccessful and the bitter taste remains in the mouth or remains as a lingering after taste if small particles of drug linger in the mouth or the tablet is caught and not swallowed.

Other methods of masking the taste include coating the drug with a polymeric material such as ethyl cellulose or a lipid based formulation such as paraffins, waxes, beeswax, higher fatty acids, higher fatty acid esters, glycerin fatty acid esters, and/or poly propylene glycols so as to create a barrier and delay the dissolution of the drug. However, these lipid based formulations are generally not effective at taste masking on their own and often require a polymer such as ethyl cellulose to complete the taste masking of the drug. These formulations are also difficult to tablet.

An example of a pharmaceutically active ingredient in which taste masking is required are analgesics which are often administered over a period of time so as to maintain a desirable and effective level of analgesia. Often, the administration is too frequent thereby necessitating a constant monitoring of the time periods. Alternatively, the dosages need to be high so that over a period of time, the level of analgesic can be maintained at a level high enough to relieve pain.

Such high doses, if delivered in tablet form, will necessitate large tablet dosage forms which include substantial amounts of excipients thereby reducing the amount of analgesic delivered per dosage form. There is no easy administration of high doses of analgesics to maintain a constant level of analgesia.

Taste masked powders may be used. However, they frequently lack sustained release properties particularly when the taste masking coat is applied by spray drying. Coatings produced by spray drying tend to be rather porous which may be suitable for taste masking but not for sustained release. (Deasey, P.B. (1984). In: Microencapsulation and Related Drug Processes, chapter 8, pp.181-192, Marcel Dekker, Inc. N.Y.)

When a powder form is used, excipients generally need not be used. Hence, the powder form provides an effective delivery system for compounds such as analgesics which need frequent or high doses. However, small particles which make up the powder have large surface areas and will release pharmaceutical too quickly. Therefore powders are generally not considered suitable for sustained release. It would be desirable if patients, requiring large dosage forms could ingest larger amounts of pharmaceutical per dose without the unpleasant taste and have the pharmaceutical released over a period to provide prolonged pain relief.

In US 4,767,789, ethyl cellulose has been used to coat acetaminophen to mask the bitter taste. However, the lower limit of ethylcellulose is 24% by weight and it is explicitly stated that taste masking of acetaminophen is not achieved if the ethyl cellulose falls below this limit. Spray drying processes used to coat acetaminophen fail to provide taste masking at low ethyl cellulose concentrations as the coat is generally porous and irregular with roughened surfaces and this leads to ineffective taste masking due to rapid release of the pharmaceutical from the dosage form.

Such low coating compositions may also affect sustained release characteristics and often to gain controlled release, dense polymer films of substantial thickness are necessary for sustained release. Porous membranes fail to provide sustained release and when coated by spray drying techniques the coating at low levels of coating polymer would tend to be rather porous, making them inadequate for taste masking and sustained release together.

It would be desirable to provide a pharmaceutical composition which provides taste masking and bioavailability of the pharmaceutical, and is capable of sustained release properties to delay release of pharmaceutical.

The present applicants have surprisingly found that a pharmaceutical can be taste masked and provide sustained release with a coating material, preferably ethyl cellulose in a powder form. Preferably the pharmaceutical is coated by using a spray drying technique.

Accordingly, it is the object of the present invention to overcome or at least alleviate one or more of the difficulties related to the prior art by providing a taste masked pharmaceutical composition capable of sustained release. This improvement may provide flexibility in bioavailability of the pharmaceutical, reduce the cost in

providing a taste masked formulation and improve the dosing regime of many pharmaceuticals requiring high doses over a period of time.

Accordingly, in a first aspect of the invention there is provided a taste masked pharmaceutical composition capable of sustained release including:

a core element including a pharmaceutically active ingredient; and

a coating material including a polymer wherein said coating material provides a substantially continuous coating on the core element.

Preferably the composition is a powder providing sustained release.

A sustained release profile allows for a slow release of the pharmaceutically active ingredient from a dosage form. Preferably the present invention provides for a reduced number of deliveries per day whilst maintaining a consistent level of pharmaceutically active ingredient.

Preferably the dosage is in 2 divided dosages/day. Most preferably the dosage is one dosage/day. However, at such large doses, the delivery of the pharmaceutical may be limiting. Tablets which are too large cannot be swallowed or require substantial amounts of excipient. The dosage required may be conveniently achieved when the taste masked pharmaceutical of the present invention is in a powder form having sustained release properties. An advantge of a powdered form is that higher doses can be administered without the need to swallow large tablet forms. The powder may be administered in the absence of other excipients (required in tablets) and carriers. The powder may be mixed in a drink or sprinkled on food.

Furthermore when sustained release compositions are pelleted and the patient bites the pellet, sustained release properties may be lost.

Accordingly in a preferred aspect, the present invention provides a sustained release and taste masked pharmaceutical composition as described above which may provide pharmaceutic control over 24 hours.

Preferably the pharmaceutical composition includes :

approximately 90% to 77%, preferably 90 to 80% by weight, based on the total weight of the composition of a core element including at least one pharmaceutically active ingredient; and

approximately 20% to 70%, by weight of a substantially continuous coating on the core element formed from a coating material including a polymer.

The core element in the coated pharmaceutical composition according to the present invention preferably may include up to 100% by weight of the pharmaceutically active ingredient.

The core element may further include carriers or excipients, fillers, flavouring agents, stabilizing agents and/or colourants. Suitable fillers may be selected from insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof. Soluble fillers may be selected from mannitol, sucrose, lactose, dextrose, sodium chloride, sorbitol and mixtures thereof.

The filler may be present in amounts of up to approximately 75% by weight based on the total weight of the composition.

The core element may be of any suitable size. Most preferably the core element has a particle size distribution with a median of about 100μm. The particles in the distribution may vary from about 1μm to about 250μm, more preferably from 25μm to about 250μm. Most preferably the particle size is 35 to 125μm. If the median of the

distribution is close to either extreme of the distribution, the taste masking or sustained release characteristics may be affected. Preferably, in a range of 25μm to 250μm, no more than 25% of particles will be less than 25μm and no more than 2% will be over 250μm.

The pharmaceutically active ingredient may be selected from any one of the following:

Antacids, anti-inflammatory substances, coronary dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrhoeal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseates, anti-convulsants, neuromuscular drugs, hyper-and hypoglycaemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough suppressants, mucolytics, anti-ulcer and anti-uricemic drugs;

Gastro-intestinal sedatives such as metoclopramide and propantheline bromide, Antacids such as aluminium trisilicate, aluminium hydroxide and cimetidine;

Anti-inflammatory drugs such as phenylbutazone, indomethicin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone, and prednisone;

Coronary vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate, peripheral;

Cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cylandelate, papaverine and nicotine acid;

Anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate hexamine hippurate, and amoxacylin and vancomycin;

Neuroleptic drugs such as flurazepam, diasepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine;

Central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride;

Antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine;

Anti-diarrheal drugs such as bisacodyl and magnesium hydroxide, the laxative drug, dioctyl sodium sulfosuccinate;

Nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine;

anti-virals such as acyclovir;

Anti-spasmodic drugs such as dicyclomine and diphenoxylate, drugs affecting the rhythm of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate;

Drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine;

Drugs used in the treatment of migraine such as ergotamine;

Drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate;

Analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid;

Anti-epileptic drugs such as phenytoin sodium and sodium valproate;

Neuromuscular drugs such as dantrolene sodium;

Substances used in the treatment of diabetes such as tolbutamide, disbenase glucagon insulin and metformin;

Drugs used in the treatment of thyroid gland disfunction such as triiodothyronine, thyroxine and propylthiouracil;

Diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and trimterone, the uterine relaxant drug ritodrine;

Appetite supressants such as fenfluramine hydrochloride, phentermine and diethylproprion hydrochloride;

Anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate;

Expectorant drugs such as guaiphenesin, cough suppressants such as dextromethorphan and noscapine;

Mucolytic drugs such as carbocisteine;

Anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine;

Decongestant drugs such as phenylpropanolamine and pseudoephedrine, hypnotic drugs such as dichloralphenazone and nitrazepam;

Anti-nauseant drugs such as promethazine theoclate;

Haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate; and

Uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid.

Particularly preferred drugs are:

Ambroxol, ibuprofen, paracetamol, 5-amino-salicylic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac, indomethicin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, co-dergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibencalamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin, potassium chloride and metoprolol tartrate.

Especially preferred drug includes paracetamol, cimetidine, dextromethorphan, ambroxol, risperidone, ibuprofen, amoxycillin, vancomycin, acyclovir, methyl phenidate, metformin and phenytoin.

The coating material may include a polymer including at least one of the following methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly (ethyl

methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), poly (hexyl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), poly (ethylene), poly (ethylene) low density, poly (ethylene)high density, (poly propylene), poly (ethylene glycol), poly (ethylene oxide), poly (ethylene terephthalate), poly(vinyl alcohol), poly(vinyl isobutyl ether), poly(viny acetate), poly (vinyl chloride) and polyvinyl pyrrolidone.

Preferably the polymer is a water insoluble polymer.

Preferably the polymeric coating material includes ethyl cellulose.

The water insoluble polymer preferably may be selected from ethyl cellulose or dispersions of ethyl cellulose acrylic and/or methacrylic ester polymers, cellulose acetates, butyrates or propionates or copolymers of acrylates or methacrylates having a low quaternary ammonium content and the like.

Preferably the polymeric coating material includes ethyl cellulose.

Preferably the coating material is between 20 to 70% the total weight of the composition. This level of coating may effectively provide taste masking and be capable of sustained release. However it is preferable that the coating material constitute less than 20% of the total composition and still provide taste masking whilst being capable of sustained release.

The coating material according to this aspect of the present invention may further include at least one plasticiser.

The plasticiser may be selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, polyethylene glycol, propylene glycol, glycerol, dibutylsebacate, castor oil and the like.

The plasticiser may be present in amounts from 0 to approximately 50% by weight based on the total weight of the coating.

The coating material according to the present invention may take any suitable form which provides a continuous coating and still provides sustained release and taste masking.

The substantially continuous coat is substantially hole-free. The substantially continuous nature of the coating may be achieved by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the coating composition including a polymer in a solvent in a drying gas having a low dew point. The dew point may preferably be less than 0°C, more preferably less than approximately -15°C.

By "substantially continuous coating" we mean a coating which retains a smooth and continuous appearance when magnified 1000 times under a scanning electron microscope and wherein no holes or breakage of the coating is evident so as to reduce taste masking.

Typical coatings may be in the range of approximately 0.005 to 25μm, preferably approximately 0.05μm to 5μm.

The solvent which may be used in the preparation of the coating of the composition may be an organic solvent. The solvent may be such that it constitutes a good solvent for the coating material but it is substantially a non-solvent or poor solvent for the pharmaceutically active ingredient. Whilst the active ingredient may partially dissolve in the solvent, in this aspect of the invention, the active ingredient will precipitate out of the solvent during the spray drying process much more rapidly than the coating material.

The solvent may be selected from alcohols such as methanol, ethanol, halogenated hydrocarbons such as dichloromethane (methylene chloride), hydrocarbons such as cyclohexane, and mixtures thereof. Dichloromethane (methylene chloride) has been found to be particularly suitable.

The concentration of polymer in the solvent will normally be less than 75% by weight. Normally the concentration will be in the range of 10-30% by weight.

Where the polymer is ethyl cellulose, the solvent is preferably methylene chloride. The concentration of ethyl cellulose is preferably in the range of 5-10% most preferably 7% by weight based on the total concentration of the coating material.

The pharmaceutically active ingredient, provided in a form suitable for coating may be suspended in the coating material/organic solvent solution, preferably in an ethyl cellulose/methylene chloride solution at a concentration in the range of 10-30% by weight, preferably in the range of 14-20% by weight.

Accordingly, the present invention further provides a taste masked pharmaceutical composition capable of sustained release including:

a core element including at least one pharmaceutically active ingredient; and

a coating material including a polymer, and

wherein the core element is selected for a size in the range of 0.1μm to 250μm and shape which facilitates coating and wherein said coating provides a continuous coating on the core element.

Applicants have found that the successful sustained release and taste masking greatly depends on the completeness of the coating on the core element. This may be influenced by parameters such as the size and shape of the core element to be coated. Where the size and shape is favourable for coating, very low levels of coating material

can be used to coat the core element such that sustained release, taste masking and a continuous coating is achieved.

The particle size distribution of the core element dictates the surface area to be coated. If the core element is too small, very large surface areas need coating.

The size of the core element is generally selected so that there will be no substantial breakage of the coat if the pharmaceutical composition is masticated so as to cause immediate release of the drug leaving a very distinctive unpleasant taste. The particles are preferably small enough to pass into curves and depressions in the mouth and between the teeth and avoid substantial breakage.

Preferably the core element has a particle size distribution of 1μm to 250μm, with a median particle size of 100μm. More preferable the distribution is from 25μm to 250μm and most preferable from 35 - 125μm. As discussed above, the particle size distribution will include particles falling outside this range. These particles can also be coated to achieve the sustained release and taste masking properties.

In a further aspect of the present invention there is provided a taste masked pharmaceutical composition capable of sustained release including:

a core element including at least one pharmaceutically active ingredient; and

a coating material including a polymer, and

wherein the core element is selected for a size in the range of 0.1μm to 250μm and shape having a low aspect ratio which facilitates coating and wherein said coating provides a continuous coating on the core element.

Shape can also influence the coverage and stability of the coat. Sharp angles on a crystal can cause weaknesses in the coat. These sharp corners may lead to

stress points on the coat and cause weaknesses in the structure possibly leading to premature release of the pharmaceutical from the pharmaceutical composition.

Where the coat is thinner at the vertices this leads to more rapid release.

The composition according to the present invention is applicable to pharmaceutically active ingredients having a crystalline morphology and particularly a low aspect ratio. The aspect ratio is a measure of the length compared to the breadth. For example, an aspect ratio of 1 would be a box or sphere. The higher the aspect ratio, the more pointy and needle-like crystals will be.

The crystal geometry may result in a relatively thin coat at the crystal needle tips the release rates may be more rapid than is preferred with such actives. Similarly, where the pharmaceutically active ingredient exhibits high water or organic solvent solubility, the release rates may be more rapid than is required in a particular application. Furthermore, areas of thin coating are susceptible to breaking and cracking and hence ineffective for sustained release and taste masking.

Applicants have found that a spherical shape of the particle is most advantageous for both stability of the coat and high payload of active pharmaceutical. Therefore, it is most preferable that the aspect ratio is less than 3, more preferably 1 to 2 and most preferably approximately 1 providing a substantially rounded shape. More preferably, the aspect ratio is 1 and the shape is round.

It is also preferable for all particles to be of the same size and shape. Inconsistencies in size and shape can lead to inconsistent coating. Where the drug particles are of different size and shape, polymeric coating materials such as ethyl cellulose will deposit differently on each particle. It is therefore preferable to have all

particles the same size and shape so that the coating process is better controlled and maintained.

Accordingly, in a preferred form, the composition may include a core element comprising approximately 30% to 80% by weight based on the total weight of the composition, said core element including:

approximately 52 to 85% by weight of a pharmaceutically active ingredient; and

approximately 5% to 25% by weight of a supplementary component selected from waxes, water insoluble polymers, enteric polymers, and partially water soluble polymers and other suitable pharmaceutical excipients.

The supplementary component may be provided as an intimate mixture with the active ingredient or as a precoat thereon. Where an intimate mixture is formed, polymers such as hydroxypropyl methyl cellulose may be used.

Where a precoat is formed, a wax coat is preferred. A paraffin wax or a canauba wax may be used. In a preferred form the pharmaceutically active ingredient is a compound of high water or solvent solubility and the supplementary component forms a precoat on the active ingredient.

By "high solubility", we mean solubility of greater than 1 in 30.

The present invention also provides a method of preparing a taste masked pharmaceutical composition capable of sustained release including :

a core element including a pharmaceutically active ingredient; and

a coating material including a polymer wherein said coating material provides a substantially continuous coating on the core element;

which method includes:

providing a sufficient amount of:

at least one pharmaceutically active ingredient selected for a size in the range of 0.1m to 250μm and shape suitable for coating to provide a continuous coating;

a solution of a coating material including a polymer and an organic solvent being selective for the polymer;

suspending or dispersing the pharmaceutically active ingredient in the solution of coating material;

spray drying the suspension or dispersion of pharmaceutically active ingredient in a dry gas having a low dew point; and

collecting the pharmaceutically active ingredient having a coating of polymeric coating material.

In a further preferred aspect of the invention, the method includes a preliminary step of pre-coating a pharmaceutically active ingredient in a shaping medium before coating with a water insoluble polymer. The size and shape of the particle is important for obtaining a coating still maintain taste masking and sustained release. Where the particles are of an inconvenient size or shape, the particle of drug may be precoated with shaping medium which may include a binder, filler, excipient or lubricant as used in the tabletting technology to obtain a size and shape suitable for coating so as to obtain an even coat which is continuous and thereby provide taste masking and sustained release.

A "shaping medium" as used herein is a compound or composition which can be shaped, manipulated or moulded in or around a body such as a pharmaceutically active ingredient such that upon shaping, manipulating and moulding, the body and shaping medium together take on a new form. The shaping, manipulating and moulding may be

used to smooth sharp angles on crystals, increase the size of the body or prepare the body so that the body is more favourably shaped for coating with polymer.

The use of wax is a suitable shaping medium and can serve to obtain a size and shape of the drug so that a favourable size and shape is obtained. For some drugs, such as pseudoephedrine, the drug may be irregular in shape, or too small. The wax serves to obtain regularity of shape, increase the size of the drug particle, or shape with the drug particle to provide a more favourable shape of particle for coating if necessary.

The wax may also serve to further delay dissolution of the drug once it enters the body or partly act to enhance taste masking. The wax may act as a hydrophobic barrier to liquids such as saliva and gastric juices.

The drug may also be incorporated in a matrix of binder and filler which can also be coated with wax to obtain a consistent size and shape suitable for coating. Suitable binders and fillers are familiar to those skilled in the art.

Wax coating of the particles can be performed by a process of preparing a slurry of molten wax which is heated to melt the wax but not degrade the pharmaceutically active ingredient. The molten slurry of wax and pharmaceutical may then be atomized preferably using a 2 fluid nozzle into a spray dryer to form core particles which may then be further coated with a coating material such as a polymer to provide taste masking.

The pharmaceutical drug may be any drug as listed previously, without limitation. It is preferable that the particles have a size distribution as listed previously and are spherical in shape having a low aspect ratio.

Spray drying of the pharmaceutically active ingredient and polymer in the solvent involves spraying a stream of air into an atomised suspension so that solvent is caused to evaporate leaving the pharmaceutical drug coated with the polymer coating material.

Preferably, for a solvent such as methylene chloride, the solvent concentration in the drying chamber is maintained above 40,000 parts, more preferably in the range of approximately 40,000 to 100,000 parts per million of organic solvent.

The spray-drying process for such solvents may be conducted at a process temperature of from approximately 5°C to 35°C.

The utilisation of a drying gas exhibiting a low dew point aids the production of a substantially continuous coating. It has also been found that the presence of a solvent during the drying step slows the evaporation rate of the solvent such that a substantially continuous coat exhibiting reduced permeability is produced. The concentration of non-solvent (e.g. water) present should be kept very low and that, in combination with the controlled drying conditions, results in microcapsules with continuous coats. These two factors may be interrelated. Thus the higher the drying gas dew point, the higher the solvent vapour pressure required in the system to give a substantially continuous coat.

The drying process may be of any suitable type.

Spray drying of the pharmaceutical compositions may be undertaken utilising either rotary, pneumatic or pressure atomisers located in either a co-current, counter-current or mixed-flow spray dryer or variations thereof.

The drying gas may be heated or cooled to control the rate of drying. A temperature below the boiling point of the solvent may be used. Inlet temperatures will typically be in the range of from approximately 40°C to 120°C and outlet temperatures approximately 5°C to 35°C.

The present invention permits the optimisation of the coat formation to meet the needs of the material or application. Adjusting the coating composition allows modification of the release profile for the material. Controlling the process parameters including temperature, solvent concentration, spray dryer capacity, atomising air pressure, droplet size, viscosity, total air pressure in the system and solvent system, allows the formation of a range of coats, ranging from dense, continuous, non-porous coats through to more porous microcapsule/polymer matrices.

The spray drying process may utilise a method employing a nozzle to atomise the drugs in polymeric coating material/organic solvent solution. Preferably pneumatic atomisation is used. The nozzle produces individual droplets with a single unit of drug suspended in a polymeric coating material/organic solvent solution. Removal of the organic solvent results in a drug dosage unit coated with the polymeric coating material.

Preferably the nozzle is a 2 fluid nozzle. The ratio of solvent/drug to air is important in a 2 fluid nozzle and this may be varied by optimizing the relative positions of the outlet and inner passages. The operating conditions include variations on air inlet temperatures, air outlet temperatures, air pressures, feed rates of solvent and drug suspensions, atomisation, air quality and outlet diameters of inlet and outlet passages of the atomizer. Preferably, the air inlet temperature is approx 70-150°C, the air outlet temperature is in the range of 20-50°C, the air flow rate is in the range of 40-1300kg/hr, the feed rates of solvent and drug is in the range of 3-75 kg/hr, atomisation air quantity is in the range of 6-60 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 2-6 mm and 4-12 mm in diameter respectively.

More preferably, the air inlet temperature is approx 100°C, the air outlet temperature is in the range of 25-35°C, the air flow rate is in the range of 40-80kg/hr,

the feed rates of solvent and drug is in the range of 8-9 kg/hr, atomisation air quantity is in the range of 7-9 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 2-3 mm and 4-6 mm in diameter respectively.

The product may be collected by any means available to the skilled addressee. Preferably the collection method is by sock filters or cyclone collection.

Accordingly, the present invention further provides in a preferred aspect a post-treatment step to remove residual solvent. The post treatment may include a post drying step including drying the final product on a tray and drying the product at a bed temperature sufficient to remove excess solvent but not degrade the pharmaceutical drug. Preferably the temperature is in the range of 35°C to 45°C, most preferably at 40°C.

The pharmaceutical composition may be in the form of a powder with a particle size distribution in the range of 0.1μm to 250μm, most preferably in the range of 35μm to 125μm. The small particle size ensures that the particles have a substantially non-gritty feel in the mouth. The small particle size may also minimise break-up of the particles in the mouth, eg by the teeth. When in the form of a powder, the pharmaceutical composition may be administered directly into the mouth or mixed with a carrier such as water, or semi-liquid compositions such as syrups, yoghurt. Preferably, the pharmaceutical composition is a powder which is mixed with water prior to ingestion.

The taste masked pharmaceutical composition may be further provided in any suitable unit dosage form. The pharmaceutical composition may be provided in a form selected from sprinkles, sachets, chewing gums, tablets; including chewable tablets, gums, lozenges, liquids, suspensions, filled capsules; including filled gelatine capsules.

Because of the sustained release characteristics of the pharmaceutical composition, it can be used as a means to treat disorders in which relief is required over a period of time. Examples of disorders include bacterial infections; pain-related disorders including arthritis, rheumatism, muscle pain; viral infections; depressants; diabetes and epilepsy. Pharmaceuticals useful in treating these disorders include antibiotics such as amoxycillin or vancomycin; analgesics such as paracetamol or ibuprofen; antivirals such as acyclovir; stimulants such as methylphenidate; antidiabetics such as metformin and antiepileptics such as phenytoin.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention as specified above.

In the figures:

Figure 1 shows the mean subject plasma profiles for 6 healthy males after ingestion of 2 x 500mg Tylenol Extra strength Tablet (fasted)(--Δ--); 1 x 1000 mg Nopap Power (fasted)(--•--); or 1 x 1000 mg Nopap Powder (fed)(-⊞-).

Figure 2 shows Predicted Steady-State Plasma Concentrations of Paracetamol (2g Dose of Nopap Powder every 12 hours). Data derived using mean plasma concentration versus time data for single dose administration of Nopap powder (Fasted) in Study SAL-1/96.

Figure 3 shows Predicted Steady-State Plasma Concentrations of Paracetamol (2g Dose of Nopap Powder every 12 hours). Data derived using mean plasma concentration versus time data for single dose administration of Nopap powder (Fed) in Study SAL-1/96.

Example 1

Paracetamol Formulation - Nopap Powder

Ethyl cellulose is dissolved in methylene chloride and then paracetamol is dispersed in the solution, in the following formulation, to produce a slurry.

Ethyl cellulose N10 NF	7% w/w
Paracetamol	28% w/w
Methylene Chloride	65% w/w

This slurry is then spray dried under the following process conditions in a NIRO "PM" type 2 fluid atomiser.

Fluid Insert	1.3mm
Air Cap	5.0mm

Feed Rate	3.0 kg/hr
Atomising gas flow rate	5 - 6 m^3/hr
Process gas Inlet Temperature	40°C
Process gas flow rate	20 m^3/hr

The final formulated product is a white, free flowing taste masked powder consisting of 80% paracetamol and 20% ethyl cellulose with a median particle size of less than 150μm.

Example 2

Pharmacokinetic Parameters from a single 1000mg dose of Tylenol Extra Strength Tablet vs Test Coated Paracetamol Powder (Nopap Powder)

A pilot study of 6 healthy males was conducted to evaluate pharmacokinetic parameters following injestion of 1000mg of a single dose of Tylenol Extra Strength Tablet (immediate release) and Test Coated Paracetamol Powder (Nopap) (sustained release, prepared according to Example 1).

METHODS

1000 mg of Tylenol® Extra Strength Tablet or Test Coated Paracetamol (Nopap) prepared according to Example 1 were administered to 6 healthy males. Plasma paracetamol concentrations were measured under fasted and fed conditions.

Tables 1, 2 and 3 summarise statistical comparisons. The arithmetic mean and individual pharmacokinetic parameters for each study treatment are shown in Table 4. Individual and mean subject plasma profiles are provided in Figure 1.

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment B versus Treatment A
(n=6)

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.739	17.244	-72.52	0.0001*	35.69	6.7 - 48.3	.	.	.
TMAX	2.917	0.582	401.43	0.0177*	3.15	231.1 - 771.7	.	.	.
AUC	39.377	46.930	-16.09	0.0227*	86.61	72.4 - 95.4	.	.	.
AUC_INF	41.863	48.137	-13.03	0.0222*	96.19	77.7 - 96.2	.	.	.
KEL	0.139	0.224	-37.92	0.0025*	49.30	44.6 - 79.6	.	.	.
THALF	5.232	3.153	65.91	0.0026*	17.28	135.2 - 196.6	.	.	.
LCMAX	1.519	2.815	-46.05	0.0001*	12.31	18.7 - 40.0	27.4	32.83	.
LAUC	3.654	3.835	-4.72	0.0227*	77.81	73.4 - 94.9	83.5	11.13	.
LAUC_INF	3.714	3.860	-3.80	0.0188*	93.59	78.1 - 95.4	86.4	8.65	.

Treatment B: 1x1000mg Nopap Powder, fasted (Batch No. 50089214) - Faulding - test
Treatment A: 2x500mg Tylenol Extra Strength tablet (Batch No. SEA704) - McNeil - reference, fasted.

Values for Treatments B and A are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Table 1

Table 2

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment C versus Treatment B
(n=6)

Parameter	Treatment Means C	B	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.050	4.739	-14.55	0.7103	5.68	9.7 - 161.2	.	.	.
TMAX	6.000	2.917	105.71	0.0044*	7.84	151.8 - 259.6	.	.	.
AUC	38.805	39.377	-1.45	0.8367	72.62	84.9 - 112.2	.	.	.
AUC_INF	42.388	41.863	1.25	0.8188	91.00	90.6 - 111.9	.	.	.
KEL	0.140	0.139	0.37	0.9796	20.08	72.2 - 128.6	.	.	.
THALF	5.348	5.232	2.23	0.8155	44.50	83.7 - 120.8	.	.	.
LCMAX	1.354	1.519	-10.83	0.4109	12.31	58.0 - 124.0	84.8	32.83	.
LAUC	3.633	3.654	-0.58	0.7497	77.81	86.1 - 111.4	97.9	11.13	.
LAUC_INF	3.725	3.714	0.30	0.8315	93.59	91.5 - 111.8	101.1	8.65	.

Treatment C: 1x1000mg Nopap Powder, fed (Batch No. 50089214) - Faulding - test
Treatment B: 1x1000mg Nopap Powder, fasted (Batch No. 50089214) - Faulding - reference

Values for Treatments C and B are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (C - B) expressed as a percentage of Treatment B

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment C versus Treatment A
(n=6)

Parameter	Treatment Means C	A	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.050	17.244	-76.51	0.0001*	35.69	2.7 - 44.3	.	.	.
TMAX	6.000	0.582	931.52	0.0001*	3.15	761.2 -1301.8	.	.	.
AUC	38.805	46.930	-17.31	0.0164*	86.61	71.2 - 94.1	.	.	.
AUC_INF	42.388	48.137	-11.94	0.0320*	96.19	78.8 - 97.3	.	.	.
KEL	0.140	0.224	-37.69	0.0026*	49.30	44.8 - 79.8	.	.	.
THALF	5.348	3.153	69.61	0.0019*	17.28	138.9 - 200.3	.	.	.
LCMAX	1.354	2.815	-51.89	0.0001*	12.31	15.9 - 33.9	23.2	32.83	.
LAUC	3.633	3.835	-5.27	0.0137*	77.81	71.8 - 92.9	81.7	11.13	.
LAUC_INF	3.725	3.860	-3.52	0.0264*	93.59	79.0 - 96.5	87.3	8.65	.

Treatment C: 1x1000mg Nopap Powder, fed (Batch No. 50089214) - Faulding - test
Treatment A: 2x500mg Tylenol Extra Strength tablet (Batch No. SEA704) - McNeil - reference, fasted.

Values for Treatments C and A are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (C - A) expressed as a percentage of Treatment A

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Table 3

Table 4

Study Design: Single dose (1000 mg) in 6 healthy volunteers with blood sampling over 24 hours.

TREATMENT A : Tylenol (fasted)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	14.032	0.67	51.18	51.88
2	17.996	0.33	53.94	55.62
3	10.011	1.5	34.29	34.96
4	19.322	0.33	49.27	50.93
5	20.513	0.33	39.9	40.97
6	21.592	0.33	53	54.46
MEAN	17.244	0.58	46.93	48.14

TREATMENT B : Nopap Powder (fasted)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	5.235	4	45.71	48.04
2	4.081	3	42.81	46.75
3	7.332	1.5	30.41	31.82
4	4.815	3.5	49.75	53.46
5	3.122	2.5	29.76	31.1
6	3.85	3	37.82	40.01
MEAN	4.739	2.92	39.38	41.86

TREATMENT C : Nopap Powder (fed)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	3.127	11	35.79	43.46
2	3.637	6	45.06	48.88
3	2.824	5	30.51	33.64
4	6.846	4	53.27	55.14
5	4.239	5	27.5	29.44
6	3.626	5	40.7	43.77
MEAN	4.050	6.00	38.81	42.39

DISCUSSION OF RESULTS

In evaluating formulations to determine bioequivalence, the 90% confidence intervals and mean ratios of the ln-transformed pharmacokinetic parameters CMAX, AUC and AUC-INF are compared.

(a) Comparison of Reference Tylenol Extra Strength Tablet (Fasted) vs Test Nopap Powder (Fasted) - refer Table 1

The 90% confidence interval and mean ratio for CMAX fell outside the allowed bioequivalence range of 80-125% and the difference was statistically significant, as would be expected for a sustained-release formulation compared with an immediate-release formulation. In fact, the mean CMAX value showed approximately a 70% reduction. Although the 90% confidence intervals for ln-transformed AUC and AUC-INF fell outside the lower limit allowed for bioequivalence and the difference was statistically significant for both parameters, the mean ratio values, which are a measure of bioavailability, were within the 80-125% "bioequivalence" range for both "extent of absorption" parameters (83.5% and 86.4% for AUC and AUC-INF, respectively). The mean TMAX values were 2.92 hours for Nopap powder and 0.58 hours for Tylenol Tablet and the difference was statistically significant, as would be expected of a sustained-release formulation compared with an immediate-release formulation.

Thus, under fasted conditions, Nopap powder exhibits sustained-release characteristics compared with Tylenol tablets with a significantly reduced rate of paracetamol absorption as evidenced by a significant reduction in CMAX and significant increase in TMAX. Only one subject, showed a reduced CMAX with Nopap powder

(fasted) compared with Tylenol Extra Strength tablet (fasted), without an increase in TMAX (1.50 hours for both formulations).

(b) Comparison of Test Nopap Powder (Fasted) vs (Fed) - refer Table 2

The 90% confidence interval for CMAX fell outside the allowed bioequivalence range of 80-125%, however, the mean ratio value (84.8%) was included in the allowed bioequivalence range. In addition, food did not cause a significant reduction in CMAX ($p>0.05$). The 90% confidence intervals for ln-transformed AUC and AUC-INF fell within the range allowed for bioequivalence, the differences were not statistically significant, and the mean ratio values, which are a measure of bioavailability, were within the 80-125% "bioequivalence" range for both "extent of absorption" parameters (97.9% and 101.1% for AUC and AUC-INF, respectively). The mean TMAX values of 6.00 hours for Nopap powder (fed) and 2.92 hours for Nopap powder (fasted) were statistically significantly different.

In accordance with FDA 1992 Bioequivalence Guidelines, for a sustained-release product to demonstrate a comparable food effect, the mean ratios of the ln-transformed least squares mean pharmacokinetic parameters AUC, AUC-INF and CMAX must fall within the 80-125% range. Therefore, based on these guidelines, Nopap powder is bioequivalent when administered under fasted and fed conditions, with the only effect of food being a significant lengthening of TMAX.

Table 3, summarises the comparison of Tylenol Extra Strength Tablet (Fasted) vs Tested Nopap Powder (Fed).

Example 3

Paracetamol Powder - Steady State Simulations

A single dose study based on results of Example 2 were used to predict 24 hour plasma concentration. Plasma concentration versus time profiles for twice daily administration of coated paracetamol powder (according to Example 1) were analysed.

In simulated studies coated paracetamol powder was administered as a dose of 2g every 12 hours. Hence, the total daily dose (4g) is in keeping with current dose recommendations for paracetamol in adults.

The results in Figure 2 show the plasma concentration-time profile using the single dose fasting data. Figure 3 shows the corresponding profile using the single dose fed data. Plasma levels would fall between these two extremes.

When dosed at a level of 2g twice a day, the plasma concentrations of paracetamol do not fall below 4mg/L and remain well below 20mg/L. As noted in a review by Prescott [Paracetamol, A Critical Bibliographic review, Taylor & Francis, London, 1996, page 228-229] the therapeutic range for effective analgesia is about 5 to 20mg/L, with a similar range for antipyretic activity.

Furthermore, during repeated administration of conventional paracetamol at a dose of 1g every 6 hours (4g a day in 4 divided doses) the mean trough plasma concentration (immediately pre-dose) was 3 mg/L, and the mean maximum concentration was about 12 mg/L [Nielson *et al.* (1991) British Journal of Clinical Pharmacology 31: 267-270]. Accordingly in the coated paracetamol the predicted steady-state levels for coated paracetamol powder are within this range (see Figures 8 and 9).

In conclusion, the preliminary results suggest that the plasma concentrations of paracetamol obtained during twice daily administration of coated paracetamol powder will be within the range of concentrations encountered with four times daily dosing with conventional paracetamol formulations. One can speculate therefore that twice daily dosing with coated paracetamol powder according to the present invention would provide good antipyretic and analgesic control over 24 hours. Perhaps the most important advantage would be overnight pain relief, particularly for patients with arthritic conditions leading to morning stiffness.

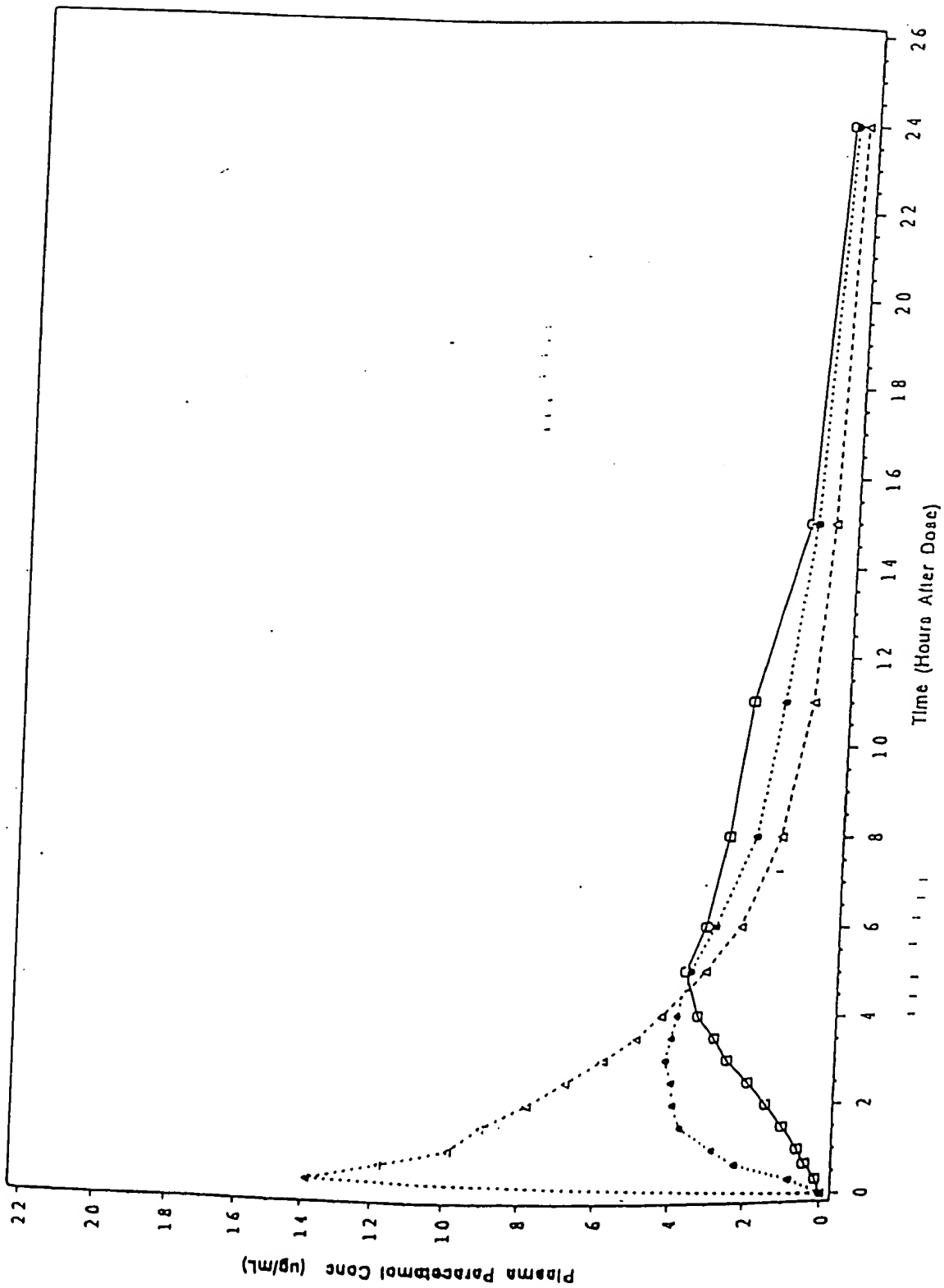
Finally it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

DATED: 23 APRIL 1997

PHILLIPS ORMONDE & FITZPATRICK

ATTORNEYS FOR: David B Fitzpatrick

F.H. FAULDING & CO. LIMTED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2
4
6
8
10
12
14
16
18
20
22
Time (Hours After Dose)
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6
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10
12
14
16
18
20
22
24
26

Figure 1

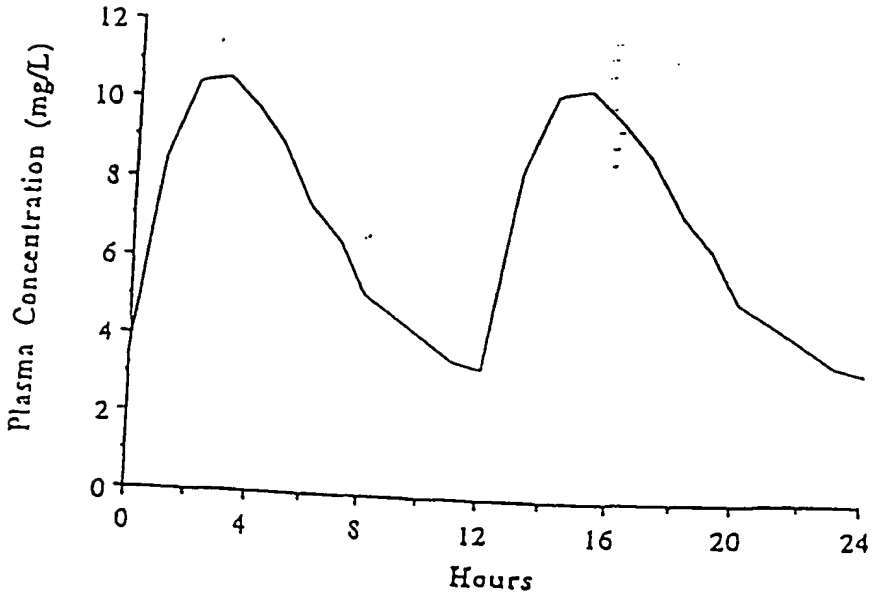

Figure 2

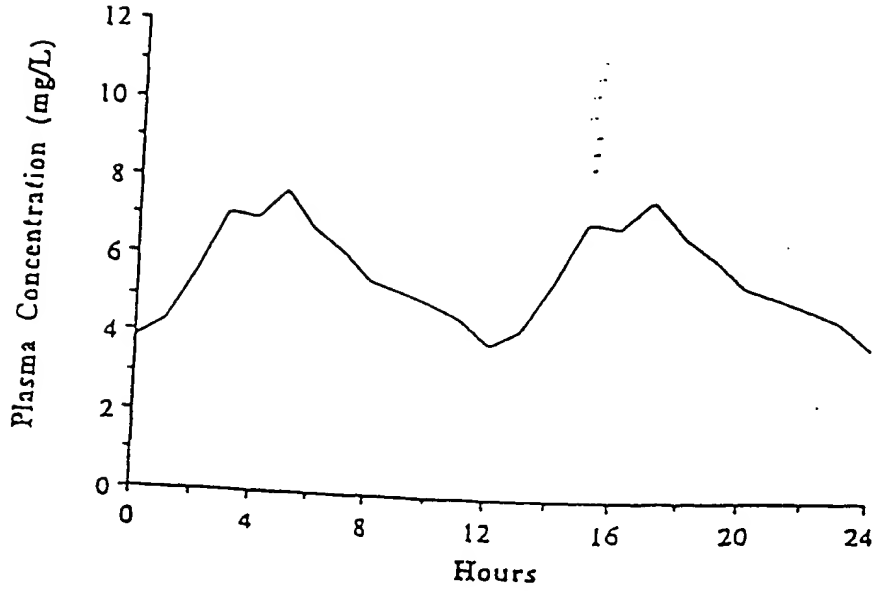

Figure 3